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# Effects of renal sympathetic denervation on heart rate variability in uncontrolled hypertensive patients with chronic kidney disease

Recently, we observed that patients with CKD stage 4 seem to be more susceptible to ventricular arrhythmias than patients without CKD, due to a larger absence of voltage, in the left ventricular walls of the first ones [1]. In agreement with previous studies, Carreira and colleagues [2] reported that heart rate variability (HRV) in the 24-h Holter was lower in patients with end stage of renal disease (ESRD) denoting impaired autonomic function [3–7]. Kidney disease induces cardiac remodeling including left ventricular hypertrophy (LVH) and heart fibrosis. Several clinical studies, including those who recruited participants with mild-to-moderate reduction in estimated glomerular filtration rate (eGFR), showed an independent association between CKD and LVH [8–11]. Specifically, there is a progressive increase in the prevalence of LVH, and left ventricular mass increased when the eGFR decreases. In addition, among participants with more advanced kidney disease on dialysis, magnetic resonance imaging (MRI) with contrast demonstrates a diffuse pattern image with gadolinium uptake suggestive of fibrosis and non-ischemic cardiomyopathy [12]. These structural changes in cardiac conduction delay ventricular activation and create late potentials in the terminal portion of the QRS complex. Furthermore, these low amplitude signals, which may be detected using a high-resolution electrocardiogram, were identified in 25% of patients on dialysis [13]. According to Brotman and colleagues in their study, time and frequency domain measures were similarly and significantly associated with ESRD and CKD-related hospitalizations, suggesting that autonomic dysfunction may be an important risk factor for ESRD and CKD-related hospitalizations [14].

Sympathetic hyperactivity is well known to increase cardiovascular risk in CKD patients and is a hallmark of an essential hypertensive state that occurs early in the clinical course of the disease [15–17]. In both conditions, hypertension and kidney failure, the mechanisms of hyperadrenergic state are varied and include reflex and neurohumoral pathways [15,16,18]. In CKD, the sympathetic hyperactivity seems to be expressed at the earliest clinical stage of the disease, showing a direct relationship with the severity of the condition of renal impairment [18–21]. The increased sympathetic tone alters renal function because of the retention volume of sodium reabsorption, a decrease in renal blood flow, and activation of the renin-angiotensin-aldosterone system [22]. Meta-analyses have shown that impaired renal function is an independent cardiovascular risk factor [23], and other studies reported that adrenergic activation exhibits an adverse impact on cardiovascular morbidity and, in the case of kidney failure, also on cardiovascular mortality [15,16,21,24]. Consequently, prevention of further damage to renal function is a therapeutic target by itself [25]. A strategy using percutaneous catheter-based delivery of radiofrequency (RF) energy was recently settled to interject the sympathetic innervation of the kidneys. This new procedure exposed no severe vascular or renal complications in the long term (up to 36 months). Our group believes that uncontrolled hypertensive patients with CKD can be benefited from the renal sympathetic denervation (RSD), regarding amelioration of the eGFR and HRV.

This prospective longitudinal study involved 24 patients with CKD stage 4 and uncontrolled hypertension. The study was conducted in agreement with the Helsinki declaration and approved by the ethics committee of our institution. All patients signed the informed consent term before inclusion. This study was conducted at the Hospital e Clínica São Gonçalo, Rio de Janeiro, Brazil. Patients were recruited from January 2015 till January 2016 from the Cardiology Service of the same hospital. Enrolled patients met the following criteria: (i) a heart with an ejection fraction of >50% as measured by echocardiography (Simpson's method), (ii) aged 18 to 80 years, (iii) patients with CKD stage 4: estimated glomerular filtration rate (eGFR) between 15 and 29 mL/min/1.73 $m^2$, calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [26], (iv) mean 24-hour ABPM ≥130/≥80 mm Hg despite treatment with non-pharmacological measures and use of at least three antihypertensive drugs (including a diuretic) on maximally tolerated doses or confirmed intolerance to medications; (v) hypertensive essential state documented at least more than one year, and (vi) the capacity to read, comprehend and sign the informed consent form, and attend the study. Patients with any of the following were excluded: (i) pregnancy; (ii) valvular disease with significant adverse sequelae; (iii) unstable angina, myocardial infarction, transient ischemic attack or stroke previously; (iv) psychiatric disease; (v) the inability to be monitored clinically after the procedure; (vi) a known addiction to alcohol or drugs that affects the intellect; (vii) congestive heart failure (symptoms of functional class II to IV heart failure on the New York Heart Association scale).

The subjects were divided into two groups according to the procedure performed: control group (n = 13) and RSD group (n = 11). Patients underwent a 24 h-Holter (Galix Biomedical Instrumentation, Florida, USA). A 3-channel recorder was used to record the electrocardiographic traces. A time domain analysis of HRV was performed, and the following parameters were obtained: a) SDNN, standard deviation (SD) of all normal RR intervals (NN); b) SDANN, SD of the averages of 5-min NN intervals over 24-h; c) rMSSD, the square root of the mean of the square of successive NN intervals; and d) triangular index (TI), integral of the density distribution (that is, the number of all NN intervals) divided by the maximum density distribution. Cutoff values adopted in the present study were derived from a previous study in which SDNN <50 ms, SDANN <40 ms, rMSSD <15 ms, and TI <15 were definitely associated with increased cardiovascular mortality in CKD patients [5]. The 24-hour ABPM [27] and the RSD procedure [28] has been described in detail previously. The patients remained hospitalized in the ward for 24 h after the procedure.

The results are expressed as a mean and standard deviation for normally distributed data and as median with interquartile range otherwise. Comparisons between two-paired values were performed with the paired *t*-test in cases of a Gaussian distribution and by the Wilcoxon

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**Table 1**
General features of patients at baseline.

| Parameters | Control group | RSD group | Overall P value |
|---|---|---|---|
| N | 13 | 11 | – |
| Age, years | 62.3 ± 12.5 | 59.7 ± 9.3 | 0.5753 |
| Body mass index, kg/m$^2$ | 26.5 ± 3.2 | 27.1 ± 3.9 | 0.6827 |
| Male gender (%) | 9 (69%) | 7 (64%) | >0.9999 |
| White ethnicity (%) | 8 (62%) | 8 (73%) | 0.6792 |
| Uncontrolled hypertension | 13 (100%) | 11 (100%) | 1.0000 |
| Coronary artery disease | 4 (31%) | 4 (36%) | >0.9999 |
| Type 2 diabetes *mellitus* | 6 (46%) | 6 (55%) | >0.9999 |
| Creatinine, mg/dL | 2.70 ± 0.21 | 2.80 ± 0.15 | 0.6643 |
| CKD stage 4 | 13 (100%) | 11 (100%) | 1.0000 |
| eGFR, mL/min/1.73 m$^2$ | 24.0 ± 4.7 | 23.3 ± 3.1 | 0.9729 |
| Albumin:creatinine ratio, mg/g | 96.5 ± 22.1 | 90.2 ± 25.8 | 0.9281 |
| Antihypertensive | | | |
| ACE-inhibitors/ARB | 13 (100%) | 11 (100%) | 1.0000 |
| Diuretics | 13 (100%) | 11 (100%) | 1.0000 |
| DHP $Ca^{++}$ channel blockers | 13 (100%) | 11 (100%) | 1.0000 |
| α-2 adrenergic agonist | 9 (69%) | 7 (64%) | >0.9999 |
| Mean 24-hour systolic/diastolic ABPM, mmHg | 134.9 ± 78.5/84.2 ± 6.6 | 136.5 ± 9.0/85.8 ± 8.5 | 0.9602/0.9222 |
| 24-hour-Holter monitoring | | | |
| SDNN, ms | 32.5 ± 4.4 | 31.6 ± 7.1 | 0.9909 |
| SDANN, ms | 26.0 ± 2.1 | 28.9 ± 5.0 | 0.4942 |
| rMSSD, ms | 8.2 ± 1.7 | 8.0 ± 1.5 | 0.9906 |
| TI | 8.4 ± 2.7 | 8.5 ± 2.6 | >0.9999 |

Values are expressed as mean ± SD; ABPM, ambulatory blood pressure measurements; ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; DHP, dihydropyridine; eGFR, estimated glomerular filtration rate; rMSSD, the square root of the mean of the square of successive NN intervals; SDANN, SD of the averages of 5-min NN intervals over 24-h; SDNN, standard deviation (SD) of all normal RR intervals (NN); and triangular index (TI), integral of the density distribution (that is, the number of all NN intervals) divided by the maximum density distribution.

test otherwise. For normality of distribution, D'Agostino-Pearson test was used. Comparisons between more than two-paired values were made by repeated-measures analysis of variance or by Kruskal–Wallis analysis of variance as appropriate, complemented by the post-hoc Tukey test. Categorical variables were compared with Fisher's exact test. A two-tailed P-value < 0.05 was used as a criterion for statistical significance. All statistical analyses were performed using the program Graphpad Prism v 7.0 (Graphpad Software, La Jolla, CA, USA).

The general features of the two groups of patients are listed in Table 1. The comparisons between the control and the RSD group, regarding mean 24-hour ABPM and renal function are displayed in Table 2. The parameters that determine the HVR recorded by the 24-hour-Holter monitoring as: SDNN (Fig. 1A), SDANN (Fig. 1B), rMSSD (Fig. 1C) and TI (Fig. 1D), from the control subjects at baseline *vs*. the 6th month of follow-up were 32.5 ± 4.4 *vs*. 33.1 ± 3.2 ms (P = 0.9938), 26.0 ± 2.1 *vs*. 26.2 ± 4.3 ms (P = 0.9998), 8.2 ± 1.7 *vs*. 8.3 ± 1.4 ms (P = 0.9996), and 8.4 ± 2.7 *vs*. 10 ± 2.8 (P = 0.4789), respectively. In the RSD group the comparisons for the same sequence of parameters at baseline *vs*. the 6th month of follow-up were 31.6 ± 7.1 *vs*. 56.7 ± 10.9 ms (P < 0.0001), 28.9 ± 5.0 *vs*. 41.6 ± 7.6 ms (P < 0.0001), 8.0 ± 1.5 *vs*. 16.9 ± 2.7 ms (P < 0.0001), and 8.5 ± 2.6 *vs*. 16.1 ± 3.2 (P < 0.0001), respectively. Comparing the both groups at the 6th month of follow-up we encountered a variation (Δ) of 23.6 ± 2.8 ms for SDNN, 15.5 ± 2.1 ms for SDANN, 8.6 ± 0.8 ms for rMSSD, and 6.2 ± 1.1 for TI (P < 0.0001 for all the comparisons).

So, we can conclude that there was a significant reduction on 24-hour ABPM, and an improvement of renal function and HRV, in patients underwent RSD. Randomized trials with a greater number of subjects are necessary.

**Table 2**
Variation (Δ) of mean systolic/diastolic 24-hour ABPM and renal function at baseline *vs*. 6th month of follow-up.

| Variable | Control (n = 13) | | RSD (n = 11) | | P value | P value |
|---|---|---|---|---|---|---|
| | Baseline *vs*. 6th month | 6th month *vs*. 6th month | Baseline *vs*. 6th month | 6th month *vs*. 6th month | Baseline *vs*. 6th month | 6th month *vs*. 6th month |
| Δ of mean systolic 24-hour ABPM, mmHg | +1.6 ± 3.2 | +1.8 ± 3.1 | −14.7 ± 3.4 | −14.9 ± 3.2 | 0.0004 | 0.0002 |
| Δ of mean diastolic 24-hour ABPM, mmHg | +1.6 ± 2.5 | +1.6 ± 2.4 | −11.4 ± 2.6 | −11.4 ± 2.5 | 0.0005 | 0.0003 |
| | Control (n = 13) at baseline | RSD (n = 11) at baseline | Control (n = 13) at 6th month | RSD (n = 11) at 6th month | P value Baseline *vs*. 6th month | P value 6th month *vs*. 6th month |
| Creatinine, mg/dL | 2.70 ± 0.21 | 2.80 ± 0.15 | 2.80 ± 0.20 | 2.40 ± 0.30 | 0.0004 | 0.0002 |
| eGFR, mL/min/1.73 m$^2$ | 24.0 ± 4.7 | 23.3 ± 3.1 | 23.0 ± 3.0 | 28.3 ± 5.0 | 0.0248 | 0.0111 |
| Albumin:creatinine ratio, mg/g | 95.5 ± 22.1 | 90.2 ± 25.8 | 100.1 ± 30.8 | 46.3 ± 20.0 | 0.0010 | <0.0001 |

Values are presented as mean ± SD; ABPM, ambulatory blood pressure measurements; eGFR, estimated glomerular filtration rate; RSD, renal sympathetic denervation.

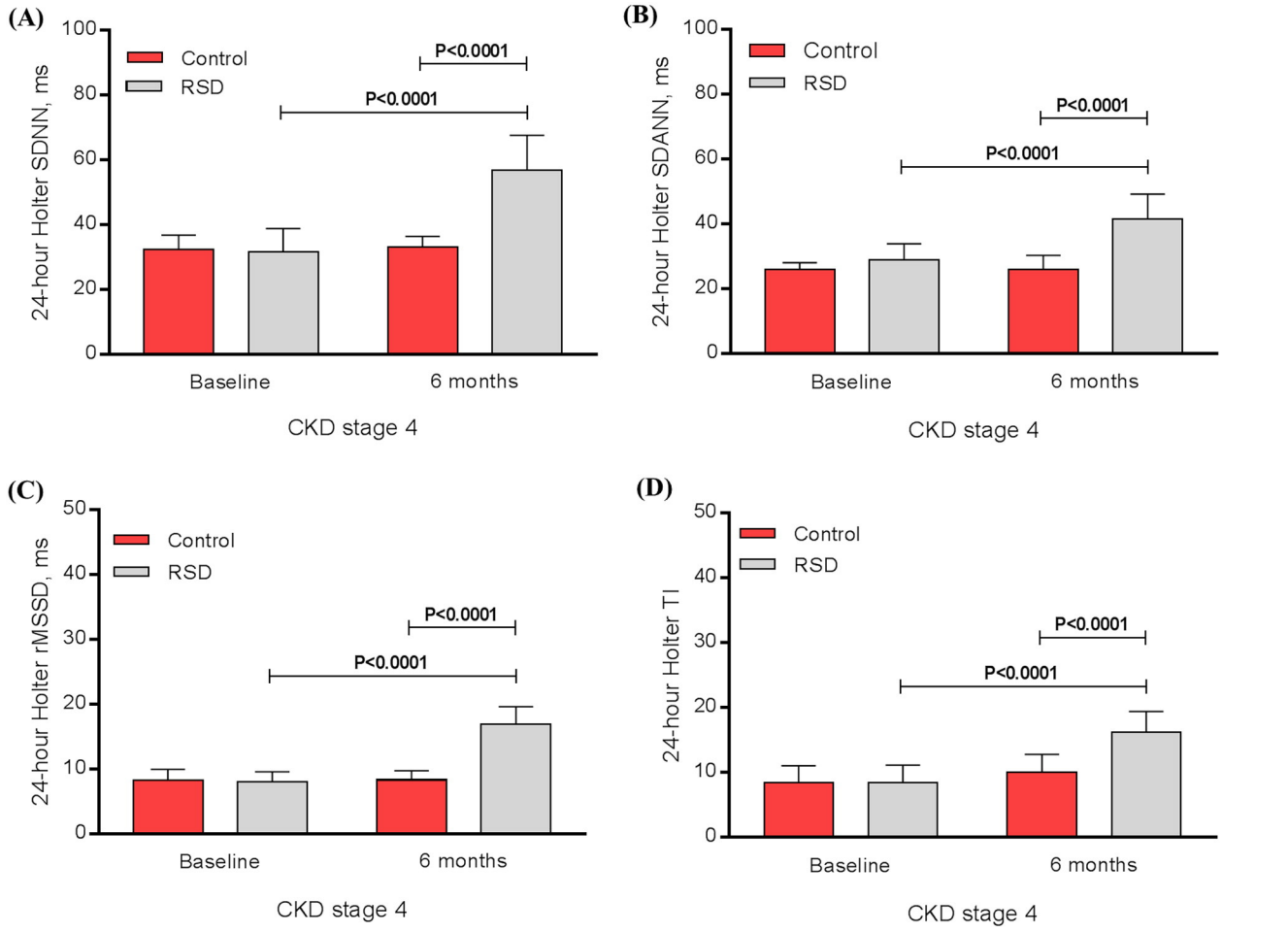


**Fig. 1.** The SDNN (A), SDANN (B), rMSSD (C) and TI (D) in control patients (n = 13) *vs.* patients underwent RSD (n = 11); CKD, chronic kidney disease; SDNN, standard deviation (SD) of all normal RR intervals (NN); SDANN, SD of the averages of 5-min NN intervals over 24-h; rMSSD, the square root of the mean of the square of successive NN intervals; and triangular index (TI), integral of the density distribution (that is, the number of all NN intervals) divided by the maximum density distribution.

## Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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